Docket No.: PF-0527-1 DIV #30

Response Under 37 C.F.R. 1.116 - Expedited Procedure
Examining Group 1642

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By: _____ Printed: Debbie Ellis

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Lal et al.

Title:	PROSTATE GROWTH-ASSOCIATED MEMBRANE PROTEINS		
Serial No.:	09/397,558	Filing Date:	September 16, 1999
Examiner:	Harris, A.M.	Group Art Unit:	1642

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REPLY BRIEF ON APPEAL

Sir:

I. INTRODUCTION

This is Appellants' Reply Brief on Appeal (submitted in triplicate) in response to the Supplementary Examiner's Answer dated May 7, 2002 ("the Supplementary Examiner's Answer") in the above-identified application (the Lal '558 application). This Reply Brief on Appeal replaces the Reply Brief on Appeal submitted on February 20, 2002, which was filed in response to the Examiner's Answer of December 7, 2001, now vacated. A Request for Oral Hearing was filed in the subject application on February 20, 2002.

On pages 1-2 of the Supplementary Examiner's Answer the Examiner stated that the "brief does not contain a statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal". Such a statement **was** provided at the top of page 2 of Appellants' Brief on Appeal of August 15, 2001.

In addition, in the Supplementary Examiner's Answer the Patent Examiner:

(1) maintained the rejection of the claims on appeal under 35 U.S.C. § 101 on the grounds that the claimed polypeptides are allegedly not supported by either a specific, substantial asserted utility or a well established utility;

(2) maintained the rejection of the claims on appeal under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement because of the invention's alleged lack of utility;

(3) maintained the rejection of claim 2 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement of the claimed polypeptide "variants";

(4) maintained the rejection of the claims on appeal under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement because undue experimentation would allegedly be required to use the claimed invention.

The Supplementary Examiner's Answer is replete with arguments made and positions taken for the first time in a misplaced attempt to justify the rejections of the claims for alleged lack of utility under 35 U.S.C. §§ 101 and 112, first paragraph. This is particularly so with respect to the substantial, specific, and credible utilities disclosed in the Lal '558 application relating to the use of the SEQ ID NO:1 and SEQ ID NO:2 polypeptides in two-dimensional polyacrylamide gel electrophoresis and in drug discovery. Such two-dimensional polyacrylamide electrophoretic gels are highly useful in a number of gene and protein expression monitoring applications, such as conducting toxicity and efficacy evaluations of drug candidates.

The Examiner's new positions and arguments include that: (a) the Lal '558 application allegedly does not disclose toxicity testing and drug discovery (Supplementary Examiner's Answer, e.g., pages 9-10); (b) the use of the claimed polypeptides in toxicology testing and drug screening is not specific or "well-established" (Supplementary Examiner's Answer, e.g., page 10); and (c) the disclosed and well-established uses of the claimed polypeptides in toxicology testing, drug development, and disease diagnosis are based on speculation, and do not constitute substantial, specific, and credible utilities (Supplementary Examiner's Answer, e.g., pages 10-13). Indeed, the Supplementary Examiner's Answer fails to acknowledge, let alone address, the Lal '558 disclosure that "[d]iagnostic assays for PGAMP include methods which utilize the antibody and a label to detect PGAMP in human body fluids or in extracts of cells or tissues" and "to monitor regulation of

PGAMP levels during therapeutic intervention" (Specification, page 33, lines 30-31; page 34, lines 15-17).

Under the circumstances, Appellants are submitting with this Reply Brief on Appeal (in triplicate) a Declaration of L. Michael Furness under 37 C.F.R. § 1.132 (the Furness Declaration). As we will show, the Furness Declaration shows the many substantial reasons why the Examiner's new positions and arguments with respect to the use of the SEQ ID NO:1 and SEQ ID NO:2 polypeptides in toxicology testing, drug discovery, and disease diagnosis, are without merit.

The fact that the Furness Declaration is being submitted in response to positions taken and arguments made for the first time in the Supplementary Examiner's Answer constitutes "good and sufficient reasons" under 37 C.F.R. § 1.195 why that Declaration was not earlier submitted and should be admitted at this time.

II. ISSUES 1 & 2 -- UTILITY REJECTIONS

A. The Lal '558 Application Discloses Substantial, Specific, and Credible Protein Expression Monitoring Utilities for the SEQ ID NO:1 and SEQ ID NO:2 Polypeptides

In this section of this Reply Brief, we will focus on the Lal '558 disclosure relating to utility of the SEQ ID NO:1 and SEQ ID NO:2 polypeptides in a number of protein expression monitoring applications that were well-known, at the time the Lal '558 application was filed, to be useful in connection with the development of drugs and the monitoring of the activity of such drugs. Furthermore, the Lal '558 application was a divisional application of and claimed priority to copending United States patent application Serial No. 09/083,521 filed on May 22, 1998 (hereinafter "the Lal '521 application") having the identical specification. Therefore, remarks herein will be directed to the Lal '521 patent application, and May 22, 1998, as the relevant date of filing. The Lal '521 disclosures in this regard are discussed at length in the accompanying Furness Declaration (at e.g., ¶¶ 3, and 10-13).

Mr. Furness is clearly highly qualified to explain the teachings of the Lal '521 application as persons skilled in the art would understand that application when it was filed on May 22, 1998.

After receiving his B.Sc. in biomolecular science from Portsmouth Polytechnic in 1984, Mr. Furness analyzed lipid methyltransferase enzymes using a variety of electrophoretic and protein analysis systems (Furness Declaration, ¶ 2). Since then he has been at the forefront of developing and using DNA microarray, nucleic acid purification, antibody, and tissue distribution technologies. In addition, he has implemented bioinformatics programs at Pfizer (United Kingdom) and Incyte with which to identify pharmacological and toxicological biological mechanisms to assist in improved drug design and development (*Id.*).

In his Declaration, Mr. Furness explained the many reasons why a person skilled in the art who read the Lal '521 application on May 22, 1998 would have understood that application to disclose the SEQ ID NO:1 and SEQ ID NO:2 polypeptides to be useful for a number of gene and protein expression monitoring applications, *e.g.*, in the use of two-dimensional polyacrylamide gel electrophoresis and western blot analysis of tissue samples in drug development and in toxicity testing. (Furness Declaration at, e.g., ¶¶ 6, and 8-13). Much, but not all, of Mr. Furness' explanations concern the use of the SEQ ID NO:1 and SEQ ID NO:2 polypeptides in two-dimensional polyacrylamide gel electrophoresis maps of the type first developed by Dr. N. Leigh Anderson and coworkers for evaluating the efficacy and toxicity of drugs, as well as for other applications (Furness Declaration, ¶¶ 10 and 12).[1]

In connection with his explanations, Mr. Furness stated that the "Lal '521 [specification] would have led a person skilled in the art in May 1998, who was using protein expression monitoring in connection with developing new drugs for the treatment of a neoplastic or reproductive disorder to conclude that a 2-D PAGE map that used the substantially purified SEQ ID NO:1 and SEQ ID NO:2 polypeptides would be a highly useful tool and to request specifically that any 2-D PAGE map that was being used for such purposes utilize the SEQ ID NO:1 and/or SEQ ID NO:2 polypeptides" (Furness Declaration, ¶ 12). For example, as explained by Mr. Furness, "[p]ersons skilled in the art would [have appreciated in May 1998] that a 2-D PAGE map that utilized the SEQ ID NO:1 and

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[1]Mr. Furness also explained, for example, why persons skilled in the art would also appreciate, based on the Lal '521 disclosure, that the SEQ ID NO:1 and SEQ ID NO:2 polypeptides would be useful in connection with developing new drugs using technology, such as Western blot analysis, that was developed independently to that of the 2-D PAGE map technology (Furness Declaration, ¶ 13).

SEQ ID NO:2 polypeptides would be a more useful tool than a 2-D PAGE map that did not utilize these protein sequences in connection with conducting protein expression monitoring studies on proposed (or actual) drugs for treating neoplastic and reproductive disorders for such purposes as evaluating their efficacy and toxicity". (*Id.*)

To support his statements quoted in the preceding paragraph, Mr. Furness provided detailed explanations, with extensive citations to pre-May 1998 publications showing the state of the art in May 1998 with respect to the use of 2-D PAGE technology to conduct gene and protein expression monitoring evaluations (Furness Declaration, ¶ 12). While Mr. Furness's explanations in paragraph 12 of his Declaration included almost three pages of text and two subparts (a)-(b), he specifically stated that his explanations in paragraph 12 were not "all inclusive" (*Id.*) For example, with respect to toxicity evaluations, Mr. Furness explained (contrary to the Examiner's apparent position in the Supplementary Examiner's Answer) how persons skilled in the art who were working on drug development in May 1998 (and for several years prior to May 1998) "without any doubt" appreciated that the toxicity (or lack of toxicity) of any proposed drug was "one of the most important criteria to be considered and evaluated in connection with the development of the drug" and how the teachings of the Lal '521 application clearly includes using differential gene and protein expression analyses in toxicity studies (Furness Declaration, ¶ 10).

Thus, the Furness Declaration establishes that persons skilled in the art who read the Lal '521 application at the time it was filed "would have routinely and readily appreciated that the SEQ ID NO:1 and SEQ ID NO:2 polypeptides would be useful tools in conducting protein expression analyses, using the 2-D PAGE mapping or western analysis techniques, in furtherance of (a) the development of drugs for the treatment of neoplastic and reproductive disorders, and (b) analyses of the efficacy and toxicity of such drugs" (Furness Declaration, ¶ 13). This, by itself, provides much more than sufficient reason to compel the conclusion that the Lal '521 application disclosed to persons skilled in the art at the time of its filing substantial, specific and credible real-world utilities for the SEQ ID NO:1 and SEQ ID NO:2 polypeptides.

Nowhere does the Examiner come to grips with the fact that, as described on pp. 23 and 34 of the '521 application, the claimed SEQ ID NO:1 and SEQ ID NO:2 polypeptides can be used to generate antibodies as highly specific probes in, for example, ELISA or western analysis – probes

that without question can be used to measure both the existence and amount of the claimed polypeptide sequences. The claimed invention is not, in that regard, some random sequence whose value as a marker for neoplastic and reproductive disorders is speculative or would require further research to determine.

Given the fact that the claimed proteins are known to be expressed, a fact explicitly stated in the application, their utility as measuring and analyzing instruments for expression levels is as indisputable as a scale's utility for measuring weight. This use as a measuring tool, regardless of how the expression level data ultimately would be used by a person of ordinary skill in the art, by itself demonstrates that the claimed invention provides an identifiable, real-world benefit that meets the utility requirement. *Raytheon* v. *Roper*,724 F.2d 951, (Fed. Cir. 1983) (claimed invention need only meet one of its stated objectives to be useful); *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999) (how the invention works is irrelevant to utility); M.P.E.P. § 2107 ("Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific, and unquestionable utility (e.g. they are useful in analyzing compounds)." (emphasis added)).

Though Appellants need not so prove to demonstrate utility, there can be no reasonable dispute that persons of ordinary skill in the art have numerous uses for information about relative gene and protein expression including, for example, understanding the effects of a potential drug for treating neoplastic and reproductive disorders. Because the patent application states explicitly that the claimed proteins are known to be expressed both in normal cells as well as cancerous tissues (Lal '521 application, e.g., at pp. 14-15), and that the proteins are known to be associated with cell growth in prostate tissue, there can be no reasonable dispute that a person of ordinary skill in the art could put the claimed invention to such use. In other words, the person of ordinary skill in the art can derive more information about a potential cancer drug candidate or potential toxin with the claimed invention than without it (see Furness Declaration at, e.g., ¶ 12, subpart (b)).

The Furness Declaration shows that a number of pre-May 1998 publications confirm and further establish the utility of 2-D PAGE maps in a wide range of drug development protein expression monitoring applications at the time the Lal '521 application was filed (Furness Declaration ¶¶ 7, 10-12; Furness Exhibits A-G). Indeed, the Anderson 1991 article and the Celis article show that the state of the art with regard to using 2-D PAGE mapping in drug effects studies would have

been well know to the skilled artisan at the time of filing the Lal '521 application. As explained by Mr. Furness, among other things (Furness Declaration, ¶ 11):

> In particular the Celis article stated that "protein databases are expected to foster a variety of biological information.... -- among others, ... drug development and testing"

Literature reviews describing the state of the art published before the filing of the Lal '521 application further confirm the claimed invention's utility. For example, the teachings in the Wilkins article state that:

> For proteome projects, the aim of this analysis [gel image analysis using computer systems] is to catalogue all spots from the 2-D gel in a qualitative and if possible quantitative manner, so as to define the number of proteins present and their levels of expression. Reference gel images, constructed from one or more gels, form the basis of two-dimensional gel databases.
> (Wilkins article, p. 26.)

Thus, the evidence overwhelmingly shows that the Lal '521 application discloses substantial, specific and credible "real-world" utilities for the SEQ ID NO:1 and SEQ ID NO:2 polypeptides. As we will show in Section II.C, *infra*, the controlling authorities require that utility based rejections under 35 U.S.C. §§ 101 and 112 be reversed in circumstances in which the patent applicant's showing of utility is much less compelling than that here.

B. The Uncontested Fact That the Claimed Polypeptides are Prostate Growth-Associated Membrane Proteins Also Demonstrates Utility

In addition to having substantial, specific and credible utilities in numerous protein expression monitoring applications, it is undisputed that the SEQ ID NO:1 and SEQ ID NO:2 polypeptides, referred to as PGAMP in the Lal '521 application, are prostate growth-associated membrane proteins, and that these proteins are related to tumor-associated antigens.

The Examiner does not dispute any of the facts set forth in the previous paragraph. Once again, however, the Examiner would require Appellants to demonstrate more, contrary to the

controlling authorities.

In the Supplementary Examiner's Answer, the Examiner takes the position that unless the Appellants can identify which particular biological functions or prostate growth-associated membrane proteins are possessed by PGAMP-1 and PGAMP-2, utility cannot be imputed. To demonstrate utility by identity as prostate growth-associated membrane proteins, the Examiner would require that all such proteins possess a common utility.

There is no such requirement in the law. In order to demonstrate utility by membership in a class, the law requires only that the class not contain a substantial number of useless members. So long as the class does not contain a substantial number of useless members, there is insufficient likelihood that the claimed invention will not have utility to justify a rejection under 35 U.S.C. § 101. That is true regardless of how the claimed invention ultimately is used and whether or not the members of the class possess one utility or many. *See Brenner* v. *Manson*, 383 U.S. 519, 532 (1966); *Application of Kirk*, 376 F.2d 936, 943 (CCPA 1967).

Membership in a protein family or class is insufficient to demonstrate utility only if the class contains a substantial number of useless members. There would be, in that case, a substantial likelihood that the claimed invention is one of the useless members of the class.

While the Appellants explained this point of law in their Brief on Appeal, the Examiner has utterly failed to address it. Beyond that, the Examiner fails to provide any basis in the Supplementary Examiner's Answer for the notion that any class must share a "common" utility for all of its members to be useful (Supplementary Examiner's Answer, pp. 12-13). The Examiner addresses PGAMP-1 and PGAMP-2 as if the protein family in which they are included is not the prostate growth-associated protein family, but rather all polypeptides, including the vast majority of useless theoretical molecules not occurring in nature, and thus not pre-selected by nature to be useful. While these "general classes" may contain a substantial number of useless members, the prostate growth-associated membrane protein family does not. The prostate growth-associated membrane protein family is sufficiently specific to rule out any reasonable possibility that PGAMP-1 and PGAMP-2 would not also be useful like the other members of the family.

Because the Examiner has not presented any evidence that the prostate growth-associated membrane protein family has any, let alone a substantial number, of useless members, the Examiner

must conclude that there is a "substantial likelihood" that the PGAMP of the claimed SEQ ID NO:1 and SEQ ID NO:2 polypeptides are useful.

Even if the Examiner's "common utility" criterion were correct – and it is not – the prostate growth-associated membrane protein family would meet it. It is undisputed that known members of the prostate growth-associated membrane protein family are tumor-associated antigens such as the prostate specific antigen PSA. A person of ordinary skill in the art need not know any more about how the claimed invention is associated with tumors to use it, and the Examiner presents no evidence to the contrary. Instead, the Examiner makes the conclusory observation that a person of ordinary skill in the art would need to know, for example, the particular biological function of a prostate growth-associated membrane protein. The Examiner then goes on to assume that the only use for PGAMP-1 and PGAMP-2 absent knowledge as to how the proteins actually work is further study of PGAMP-1 and PGAMP-2 themselves.

Not so. As demonstrated by Appellants, knowledge that PGAMP-1 and PGAMP-2 are prostate growth-associated membrane proteins is more than sufficient to make them useful for the diagnosis and treatment of neurodegenerative disorders and cancer. Indeed, PGAMP-1 and PGAMP-2 have been shown to be expressed in cancer cells. The Examiner must accept these facts to be true unless the Examiner can provide evidence or sound scientific reasoning to the contrary. But the Examiner has not done so.

What the Examiner is really trying to do here is to raise the threshold of utility for biotechnological inventions above that of all other inventions. If the Examiner's heightened standard were the law, it would not be enough to demonstrate that a new fishing rod catches fish. The Examiner would require the applicant to prove exactly what kinds of fish the rod could be used to catch.

The law forbids treating biotechnological inventions differently from other inventions. *In re Gazave*, 379 F.2d 973, 977-78 (CCPA 1967) (quoting *In re Chilowsky*, 299 F.2d 457, 461 (CCPA 1956)). Appellants accordingly ask that the PTO apply to the claimed invention the same standards it applies to all other inventions – the standard that is required by law.

C. **The Supplementary Examiner's Answer is Based on Flawed Assumptions About the Legal Standard for Utility**

In the face of Appellants' demonstration of numerous disclosed and well-established utilities for the claimed SEQ ID NO:1 and SEQ ID NO:2 polypeptides, the Supplementary Examiner's Answer does not offer any facts or sound scientific reasoning as would be required to overcome the presumption of utility that must be attributed to the claimed invention as a matter of law. For example, the Supplementary Examiner's Answer has no answer for the disclosed utilities of the SEQ ID NO:1 and SEQ ID NO:2 polypeptides in drug screening analyses and in two-dimensional electrophoretic gel analyses that are discussed in section II.A of this Reply Brief on Appeal.

Also pertinent are the explanations in the Furness Declaration (at, e.g., ¶¶ 10 and 12) regarding why persons skilled in the art, who read the Lal '521 application at the time it was filed, would have (a) concluded that the SEQ ID NO:1 and SEQ ID NO:2 polypeptides would be highly useful tools for inclusion in a 2-D PAGE map for evaluating the efficacy and toxicity of proposed drugs for neoplastic and reproductive disorders, and (b) requested specifically that any 2-D PAGE map that was being used for such purposes to utilize the SEQ ID NO:1 and/or SEQ ID NO:2 polypeptides. These explanations show, beyond any doubt, that the SEQ ID NO:1 and SEQ ID NO:2 polypeptides are highly useful tools in gene and protein expression monitoring applications used in connection with the development of drugs to treat neoplastic and reproductive disorders.

The Examiner has not and cannot provide **any** evidence tending to show that a person of ordinary skill in the art could not achieve the disclosed utilities, or indeed that any experimentation whatsoever would be required to put the claimed invention to beneficial use. And the Supplementary Examiner's Answer utterly fails to address the Appellants' overwhelming evidence demonstrating not only that persons of ordinary skill in the art recognize the utility of inventions such as those claimed, but also that the likelihood that the claimed invention would achieve those utilities is far beyond substantial.

Apart from ignoring the presumption of utility and the Examiner's burden to overcome it, the entirety of the Supplementary Examiner's Answer ultimately is based on three flawed assumptions. They are:

i. the claimed invention cannot be proven to be useful until the biological role or function of the claimed protein also is proven;

ii. assignment to a family whose members are known to be useful does not establish utility unless the members share a single, common utility; and,

iii. the *Brenner* v. *Manson* case somehow supports the Examiner's position in the present situation.

All of these assumptions are incorrect.[2]

1. The Precise Biological Role Or Function of a Protein is Not Required To Demonstrate Utility

Rather than responding to Appellants' evidence demonstrating utility, the Examiner attempts to dismiss it altogether by arguing that the disclosed and well-established utilities for the SEQ ID NO:1 and SEQ ID NO:2 polypeptides are not "specific, substantial, asserted" utilities. (Examiner's Answer at pages 4-7 and 9-11). The Examiner is incorrect both as a matter of law and as a matter of fact.

The basis of the Examiner's argument is that, without information as to the precise biological role of the claimed invention, the claimed invention's utility is not sufficiently specific or substantial. According to the Examiner, it is not enough that a person of ordinary skill in the art could use and, in fact, would want to use the claimed invention either individually or in a competitive drug screening assay for such applications as the evaluation of a drug's efficacy and toxicity. The Examiner would require, in addition, that the applicant provide a "specific and substantial interpretation" of the results generated in any given expression analysis.

It may be that "specific and substantial interpretations" and detailed information on biological function are necessary to satisfy the requirements for publication in some technical journals, but they

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[2]It is respectfully submitted that the entirety of the Examiner's alleged rebuttal of Appellants' arguments and reasoning in the Supplementary Examiner's Answer are based on these three incorrect assumptions. Nevertheless, to the extent that Appellants do not specifically rebut these points on a line-by-line basis, this is not to be construed as acquiescence to their veracity, and Appellants do not waive the right to rebut them individually at any later point in the proceedings.

are not necessary to satisfy the requirements for obtaining a United States patent. The relevant question is not, as the Examiner would have it, whether it is known how or why the invention works, *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999), but rather whether the invention provides an "identifiable benefit" in presently available form. *Juicy Whip Inc.* v. *Orange Bang Inc.*, 185 F.3d 1364, 1366 (Fed. Cir. 1999). If the benefit exists, and there is a substantial likelihood the invention provides the benefit, it is useful. There can be no doubt, particularly in view of the Furness Declaration (at, *e.g.*, ¶¶ 10 and 12), that the present invention easily meets this test.

The threshold for determining whether an invention produces an identifiable benefit is low. *Juicy Whip*, 185 F.3d at 1366. Only those utilities that are so nebulous that a person of ordinary skill in the art would not know how to achieve an identifiable benefit and, at least according to the PTO guidelines, so-called "throwaway" utilities that are not directed to a person of ordinary skill in the art at all, do not meet the statutory requirement of utility. Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001).

Knowledge of the biological function or role of a biological molecule has never been required to show real-world benefit. In its most recent explanation of its own utility guidelines, the PTO acknowledged as much (66 F.R. at 1095):

> If all the requirements under 35 U.S.C. 112, ¶1, are met, there is no statutory basis to require disclosure of why an invention works or how it was developed. "[I]t is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works." *Newman* v. *Quigg*, 877 F.2d 1575, 11 USPQ2d 1340, 1345 (Fed. Cir. 1989).

Biological role or function is, instead, merely one factor that can be relevant in demonstrating whether there is a "substantial likelihood" a claimed invention can achieve the identified benefits. It may be particularly helpful in those cases where it is necessary to prove that the identifiable benefit of one biological composition can be imputed to another. In these cases, see, *e.g.*, *Brana*, 51 F.3d at 1560, 1565-1566, because there is no direct evidence that the biological composition can achieve any given utility, knowledge of biological function can be used to prove a "substantial likelihood" of utility indirectly, by association. Biological function serves as a link between a compound whose utility otherwise would be unknown and another compound having known utility. If, for example, a prior art biological composition is known to be a target in the treatment of disease, one way the

applicant can prove utility is by demonstrating that the claimed invention is substantially likely to share the utility for disease treatment because it also shares a biological role with the prior art composition.

But in other cases, such as this one, proof of biological function is not necessary. In those cases, the evidence already is sufficient to show that there is a substantial likelihood that the claimed invention produces the alleged benefit. The claimed invention has a known utility whether or not it can be linked (through biological function) with some other composition.

By implicitly requiring knowledge of biological function for any claimed protein, the Examiner has, contrary to law, elevated what has long been acknowledged to be an evidentiary factor into an absolute requirement of utility. Rather than looking to the biological role or function of the claimed invention, the Examiner should have looked first to the benefits it is alleged to provide.

Finally, there is no basis for the Examiner's assertions, stated for the first time in the Supplementary Examiner's Answer, to the effect that the use of the SEQ ID NO:1 and SEQ ID NO:2 polypeptides as targets in two-dimensional gel electrophoresis assays, absent correlation between the proteins and specific diseases, would generate expression profile information that would require the artisan "to perform further experimentation on the claimed material itself in order to determine to what 'use' any expression information regarding this polypeptide could be put" (Supplementary Examiner's Answer, page 10). When used, for example, for evaluating the efficacy or toxicity of a drug, expression profile information obtained from a two-dimensional electrophoretic gel is used to evaluate and characterize human response to the **drug**, not the claimed invention. It simply does not matter whether or not there is a correlation between any or all of the probes of the two-dimensional electrophoretic gel with a particular disease. Moreover, as explained in the Furness Declaration (at ¶ 12), a person skilled in the art reading the Lal '521 application on May 22, 1998, would have concluded that the SEQ ID NO:1 and SEQ ID NO:2 polypeptides would be highly useful tools to include in a 2-D PAGE map in connection with working on new drugs for treating neoplastic and reproductive disorders.

2. Assignment to a Family Whose Members are Useful Establishes Utility

For the reasons discussed in Section II.B, *supra*, the Examiner cannot properly impose a

"common utility" requirement with respect to the prostate growth-associated membrane protein family to which PGAMP-1 and PGAMP-2 belong. The Examiner's attempt to do so, if permitted to succeed, would improperly raise the threshold of patentable utility for biotechnological inventions to a point above that of other classes of inventions.

3. The Examiner's Reliance On *Brenner* v. *Manson* Is Misplaced

This is not a case in which biological function is necessary to provide a link between the claimed invention on one hand, and a compound of known utility on the other. Given that the claimed invention is disclosed in the Lal '521 application to be useful as a tool in a number of drug screening applications that were well-known at the time of the filing of the application in connection with the development of drugs and the monitoring of the activity of drugs, its precise biological function is superfluous information for the purposes of establishing utility.

The uncontested fact that the claimed invention already has a disclosed use as a tool in then available technology (such as drug screening assays or two-dimensional gel electrophoresis assays) distinguishes it from those few claimed inventions found not to have utility. In each of those cases, unlike this one, the person of ordinary skill in the art was left to guess whether the claimed invention could be used to produce an identifiable benefit. Thus the Examiner's unsupported statement that one of those cases, *Brenner* v. *Manson*, 383 U.S. 519, 532, 534-35 (1966), is somehow analogous to this case is plainly incorrect.

Brenner concerns a narrow exception to the general rule that inventions are useful. It holds that where the assertion of utility for the claimed invention is made by association with a group including useful members, the group may not include so many useless members that there would be less than a substantial likelihood that the claimed invention is in fact one of the useful members of the group. In *Brenner*, the claimed invention was a process for making a synthetic steroid. Some steroids are useful, but most are not. While the claimed process in *Brenner* produced a composition that bore homology to some useful steroids, anti-tumor agents, it also bore structural homology to a substantial number of steroids having no utility at all. There was no evidence that could show, by substantial likelihood, that the claimed invention would produce the benefits of the small subset of

useful steroids. It was entirely possible, and indeed likely, that the claimed invention was just as useless as the majority of steroids.

In *Brenner*, the steroid was not disclosed in the application for a patent to be useful in its then-present form. Here, in contrast, the claimed invention is a protein that was disclosed to be useful in the Lal '521 application for many known applications involving protein expression analysis. Its utility is not a matter of guesswork. They are not random polypeptide sequences that might or might not be useful as scientific tools. Unlike the steroid in *Brenner*, the utility of the invention claimed here is not grounded upon being structurally analogous to a molecule which belongs to a class of molecules containing a significant number of useless compositions. While not necessary to reverse the Examiner's rejections, because the SEQ ID NO:1 and SEQ ID NO:2 polypeptides are human proteins, it is more likely than not that they belong to the class of molecules that have been pre-selected by nature to be useful.

And, contrary to the unsupported assertion of the Examiner (Supplementary Examiner's Answer, page 7), the utilities disclosed in the Lal '521 application are for purposes other than just studying the claimed invention itself, *Brenner*, 383 U.S. at 535, i.e., for other (non self-referential) uses such as to ascertain the toxic potential of a drug candidate and to study the efficacy of a proposed drug. Indeed, in view of the Furness Declaration (at, e.g., ¶ 12), the evidence shows that persons skilled in the art on May 22, 1998, who read the Lal '521 application, would have believed the SEQ ID NO:1 and SEQ ID NO:2 polypeptides to be so useful that they would request them to be included as probes in drug screening analyses in association with identifying drugs for treating neoplastic and reproductive disorders.

Accordingly, in this case, biological function is in fact superfluous information for the purposes of demonstrating utility. Here, the claimed invention is more than "substantially likely" to be useful, in a way that is utterly independent of knowledge of precise biological function, as the Furness Declaration and other evidence presented by the Appellants demonstrates. Given that the claimed invention has disclosed and well-established utilities, the Appellants need not demonstrate utility by imputation.

In the end, the Examiner has failed to recognize that new technologies, such as those involving the use of two-dimensional polyacrylamide gel electrophoresis to conduct protein

expression analyses, have made useful biological molecules that might not otherwise have been useful in the past. *See Brenner*, 383 U.S. at 536. Technology has now advanced well beyond the point that a person of ordinary skill in the art would have to guess whether a newly discovered expressed polynucleotide or protein could be usefully employed without further research. It has created a need for new tools, such as the claimed SEQ ID NO:1 and SEQ ID NO:2 polypeptides, that provide, and have been providing for some time now, unquestioned commercial and scientific benefits, and **real-world benefits** to the public by enabling faster, cheaper and safer drug discovery processes. The Examiner is obliged, by law, to recognize this reality.

III. ISSUE 3 -- ENABLEMENT REJECTION OF POLYPEPTIDE VARIANTS

In maintaining the rejection of the claimed polypeptide variants for alleged lack of enablement, the Examiner ignores the arguments presented in Appellants' Brief on Appeal. The Examiner continues to insist that the claimed subject matter encompasses "a large genus of molecules" which represent "a variety of subgenera with widely varying attributes" (Supplementary Examiner's Answer, page 8). This is incorrect.

Claim 2 recites not only that the polypeptides have at least 90% sequence identity to either SEQ ID NO:1 or SEQ ID NO:2, but also have "**a naturally-occurring amino acid sequence**." Through the process of natural selection, nature will have determined the appropriate amino acid sequences. Given the information provided by SEQ ID NO:1 (the amino acid sequence of PGAMP-1), SEQ ID NO:2 (the amino acid sequence of PGAMP-2), SEQ ID NO:3 (the polynucleotide sequence encoding PGAMP-1), and SEQ ID NO:4 (the polynucleotide sequence encoding PGAMP-2), one of skill in the art would be able to routinely obtain "a naturally-occurring amino acid sequence having at least 90% amino acid sequence identity to" SEQ ID NO:1 or SEQ ID NO:2. For example, the identification of relevant polynucleotides could be performed by hybridization and/or PCR techniques that were well-known to those skilled in the art at the time the subject application was filed and/or described throughout the Specification of the instant application. See, e.g., page 34, lines 18-30; and Example VI at page 45. Thus, one skilled in the art need not make and test vast numbers of polypeptides that are based on the amino acid sequences of SEQ ID NO:1 or SEQ ID NO:2. Instead, one skilled in the art need only screen a cDNA library or use

appropriate PCR conditions to identify relevant polynucleotides/polypeptides that already exist in nature.

As set forth in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971):

> The first paragraph of § 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.
>
> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Contrary to the standard set forth in *Marzocchi*, the Examiner has failed to provide any **reasons** why one would doubt that the guidance provided by the present Specification would enable one to make and use the recited variants of SEQ ID NO:1 and SEQ ID NO:2. Hence, a *prima facie* case for non-enablement has not been established with respect to the recited variants of SEQ ID NO:1 and SEQ ID NO:2.

For at least the above reasons and the reasons presented in the Brief on Appeal, reversal of this rejection is requested.

IV. ISSUE 4 -- ENABLEMENT REJECTION FOR UNDUE EXPERIMENTATION

In maintaining the rejection of the claimed polypeptides for alleged lack of enablement, the Examiner continues to focus on a misguided requirement for knowledge of precise biological function. The Examiner insists that "since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility ... one skilled in the art would not know how to use the claimed invention so that it would operate as intended without undue experimentation" (Supplementary Examiner's Answer, page 7). It is clear that, based on the arguments presented in the Brief on Appeal, the Declaration of Furness, and above, the claimed invention has at least one patentable utility that was well established at the time of filing of the original patent application (May

22, 1998; the filing date of the Lal '521 application). One of ordinary skill in the art would know how to use the claimed invention as, for example, toxicology controls in drug discovery.

Despite this, the Examiner continues to err in insisting that undue experimentation would be required to practice the claimed invention. The Examiner provides no objective evidence or sound scientific reasoning to show that the claimed polypeptides could not be used as, for example, toxicology controls in drug discovery, or in any other manner asserted by the Appellants. Therefore, the Examiner has not met the burden to establish a *prima facie* case of lack of enablement.

For at least the above reasons and the reasons presented in the Brief on Appeal, reversal of this rejection is requested.

V. CONCLUSION

For all the foregoing reasons and the reasons stated in the Appellants' Brief on Appeal, it is submitted that the Examiner's rejections of the claims on appeal should be reversed.

If the USPTO determines that any additional fees are due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108**.

This form is enclosed in triplicate.

Respectfully submitted,

INCYTE GENOMICS, INC.

Date: May 31, 2002.

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Limited Recognition (37 C.F.R. § 10.9(b)) attached
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